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EXAMINER	
HAQ, SHAFIQUL	

ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/062,131	RUSSELL, JOHN C.	
	Examiner	Art Unit	
	SHAFIQUL HAQ	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/20/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1 and 30 are pending in the application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1 and 30 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification while being enabling for First and Second macromolecule having activated reactive group(s) to form covalent bond as required, do not reasonably provide enablement to form covalent bond formation with all Macromolecules that not having any reactive groups.

The step d) of claims 1 and 30 require contacting the complex comprising the First Macromolecule bound to the reactive surface that is formed in step b) with at least one Second Macromolecule to form a stable complex comprising the reactive surface, the first Macromolecule, and at least the Second macromolecules wherein a covalent bond existing between the First Macromolecules and the at least one Second Macromolecules. The claim as recited requires the First Macromolecule be capable of forming a disruptable bond with the reactive surface but the claim as

claimed does not require the First and Second Macromolecule having any reactive group or activated reactive group for forming a covalent bond between them i.e. as claimed the Second Macromolecule can be any macromolecule and does not require any reactive group, activated reactive group or linker group and the First Macromolecule can be any macromolecule capable of forming a disruptable bond with the reactive surface but does not require any reactive group, activated reactive group or a linker group for forming a covalent bond with the Second Macromolecule.

Specification teaches that the solid, First Macromolecule, Second Macromolecule, and any other macromolecules to be joined to the Macromolccular Conjugate can be reacted with a bifunctional linker or a polyfunctional linker, and preferably a heterobifunctional linker having at least two reactive moieties that can be differentially reacted or activated and reacted. Another option is to treat one or more macromolecules to be joined to the conjugate with reagents that expose a previously hidden or unavailable active group, such as, without limitation, contacting a protein or other macromolecule with dithiothreitol (DTT) to expose sulfhydryl moieties, which are suitably reactive (paragraph [0031]).

However, while the specification is enabled for a macromolecule activated with a reactive functional group to form covalent bond with a second macromolecule having a reactive moiety capable of reacting with the activated reactive functional group of the first macromolecule, do not provide enablement for association of all first and second macromolecules without having reactive moieties and without activating at least one of the macromolecule with a reactive functional group. As for example, an

antibody against BSA (i.e. first macromolecule) can be linked to a solid support having hydrazide reactive surface to form hydrozone or oxyamino linked molecules using carbohydrate domain (carboxylic functional group activated to form aldehyde) of the antibody (that is not involved in antigen binding). The surface immobilized antibody so formed, when contacted with BSA antigen (i.e. second macromolecule) will bind to the BSA antigen, but there will not be any covalent bond existing in between the antibody and the BSA antigen as antibody-antigen binding do not involve covalent bond formation. Similarly, a BSA molecule (after reduction to expose sulfydryl groups) can be immobilized on a maleimide activated surface and the immobilized BSA then when contacted with a second BSA molecule (i.e. second macromolecule) or other protein (i.e. second macromolecule; e.g. protein having amino functional group or having thiol group), will not form any covalent linkage with first BSA molecule..

Therefore, the specification fails to provide sufficient support of the broad use of all macromolecules without regard to having an at least one activated functional group on one of the macromolecule capable of forming a covalent bond with a second macromolecule having a reactive group reactive with the activated functional group. As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of all Macromolecules to find Macromolecules that are suitable to form covalent bond without any activated functional group and specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Undue experimentation

would be required to practice the invention as claimed due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1 and 30 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz {US 2003/0013857}.

Schwartz describes a method of attaching a protein to a functionalized solid surface through a hydrazone linkage to form a solid surface-protein complex as described in steps a) through c) of claims 1 and 30 of this application wherein hydrazide-containing macromolecules (e.g. proteins) are immobilized to a functionalized solid support via hydrazone bond formation. Schwartz discloses solid

support modified with hydrazide linkers (see paragraphs [0018], [0112], 0134-0135], [0146-0147] and [0150]) which, when reacted with molecules (e.g. proteins, peptides, polynucleotides) possessing carbonyl group forms hydrozone linked molecules (see paragraphs [0144], [0147], [0148] and [0175]) that are cleavable (paragraph [0110]) i.e. molecules (i.e. proteins, peptides, polynucleotides) linked to a solid support with a cleavable linkages (e.g. hydrazone) are disclosed by Schwartz. **Schwartz further discloses that cleavable linkages have been used to isolate receptors (i.e. second macromolecule) following covalent linking between a ligand (i.e. first macromolecule) and a receptor (paragraphs [0109] and [0110]).** Schwartz also discloses binding of antibody (i.e. first macromolecule) to hydrazide modified surface using carbohydrate domain of the antibody (that is not involved in antigen binding) to form a hydrazone or oxyamino bond and thus keeping the antibody active site available for binding with antigen (second macromolecule) (paragraph [0180]).

The Schwartz method does not specifically describe a step corresponding to step d) of claims 1 and 30 of this application wherein the protein ('First Macromolecule') is covalently linked to another protein ('Second Macromolecule") and cleaving the first macromolecules from the surface without cleaving the covalent bond between the first macromolecules and the at least one second macromolecule.

Given the fact the biomolecules (binding partners e.g. antibody, receptors) can be linked to solid support through acid cleavable hydrazone linkages (e.g. hydrazone bond) (Schwartz et al.) and given the generic discussion that other conventional

methods are known for covalently linking biomolecules to one another as in the example of Schwartz wherein biomolecules linked to solid support can be linked to other proteins or analytes (e.g. antigen) by conventional methods (i.e. different covalent bonding) and given the teaching that cleavable linkages have been used to isolate receptors (i.e. second macromolecule) following covalent linking between a ligand (i.e. first macromolecule) and a receptor (paragraphs [0109] and [0110]), it would be obvious to one of ordinary skill in the art at the time the invention was made to use the hydrazine modified support of Schwartz to immobilize a binding partner (e.g. antibody or ligand i.e. first macromolecule) through a cleavable linkage (e.g. hydrazone) to capture complementary binding partner (e.g. antigen or receptor i.e. second macromolecule) for subsequent cleavage of the binding complex from the solid surface for purification and for further analysis.

The limitation of claim 30 of this application, i.e. the "First Molecule having a molecular weight of at least 2,000 daltons", relates to a molecular weight range conventionally associated with antibodies (a class of proteins).

Response to Argument

6. Applicant's arguments filed October 27, 2008 regarding the Schwartz patent have been fully considered but they are not persuasive to overcome the rejection under 35 USC 103. Moreover, a further review of the claims necessitated rejections under 35 USC 112 first paragraph as described in this office action.

Applicant argued that in present application the linker between the first macromolecule and the solid support is cleavable while the linker between the first macromolecule and the at least second macromolecule is not cleavable and argued that if the bond between the First macromolecule and the second macromolecules were cleavable, the conjugate would no longer exist after the complex comprising the first macromolecules and the second macromolecules is detached from the solid support. Applicants argued that Schwrtz does not describe the preparation of conjugates comprising two macromolecules using conventional bifunctional reagents. Applicants further argued that Schwartz teaches away from the method described herein because Schwartz calls for the cleavage of the first macromolecule (protein) from the second macromolecule (protein), which cleavage would destroy the conjugate. Applicants further argued that both a cleavable linker and a non-cleavable linker are required in the method described herein, and Schwartz fails to disclose or suggest the use of a non-cleavable linker and it is clear that the methods recited in claims 1 and 30 do not result in cleavage of the linker between the first and second macromolecule.

Applicants' arguments have been fully considered but are not found convincing. In response to Applicants statement that in present application "the linker between the first macromolecules and the solid support is cleavable while the linker between the first macromolecule and the at least second macromolecule is not cleavable", it is noted that the features upon which applicant relies (i.e. the linker between the first macromolecules and the solid support is cleavable while the linker between the first

macromolecule and the at least second macromolecule is not cleavable) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims recite that a covalent bond exists between the first macromolecule and the second macromolecule but do not recite that the bond is not cleavable. The claims discloses disruption of the bond between the reactive surface and the first macromolecule without disrupting the covalent bond existing between the first macromolecule and the at least one second macromolecule, but this does not mean that the bond between the first and second macromolecules in not disruptable. The bond between the first macromolecule and the second macromolecule is not limited to a particular covalent bond and thus a condition (i.e. reaction condition) at which it disrupts the bond between the first macromolecule and the solid support may not disrupt the bond between the first macromolecule and the second macromolecule but at other condition it may be disruptable. With regard to bifunctional reagent, Schwartz teaches aliphatic and aromatic crosslinking compounds comprising various functionalities (see paragraphs 0007, 0008 and 0012) which would encompass different conventional and non-conventional linkers/bonds and the bond between the macromolecules in not limited to a particular type of bond. It is not the bond/linkers itself that determines cleavage, the reaction condition is also important which determines what type of bonds/linker would be cleavable. As for example, if a first biomolecule is linked to a surface through a thiol (e.g. gold sulfur) bond and the

second biomolecule is attached to the first biomolecules through a photocleavable bond or a hydrazino bond, than a reaction condition that breaks the gold-sulfur bond would not cleave the photocleavable bond or the hydrazine bond and similarly, a condition that cleaves the photocleavable bond or hydrazino bond between the may not be suitable to cleave the gold-sulfur bond.

With regard to Schwartz's disclosure of macromolecular complex, Schwartz discloses solid support modified with hydrazide linkers (see paragraphs [0018], [0112], 0134-0135], [0146-0147] and [0150]) which, when reacted with molecules (e.g. proteins, peptides, polynucleotides) possessing carbonyl group forms hydrozone linked molecules (see paragraphs [0144], [0147], [0148] and [0175]) that are cleavable (paragraph [0110]) i.e. molecules (e.g. proteins, peptides, polynucleotides) linked to a solid support with a cleavable linkage. Schwartz teaches different cleavable linkages such as acid cleavable, photocleavable and disulfide bonds (column 0109) and teaches that the cleavable linkages can be used to isolate receptors following covalent linking between a ligand and a receptor (paragraphs [0109] and [0110]). Schwartz teaches solid support for immobilization of biomolecules and the immobilized biomolecules may be used in diagnostic and therapeutic application (paragraph 0018). Schwartz specifically teaches conjugates comprising protein conjugate with bacterial polysaccharide to be used as vaccine, which does teach macromolecules "conjugated together" for use in therapeutic application and which does not call for the cleavage of the first macromolecule (i.e protein) from the second macromolecule (i.e. bacterial polysaccharide) (paragraph

0017) as Applicants argued and therefore, Schwartz does not teaches away having conjugated macromolecules separated from solid phase.

Therefore, given the fact the biomolecules can be linked to solid support through cleavable linkages (Schwartz et al.) and given the generic discussion that other conventional methods are known for covalently linking biomolecules to one another as in the example of Schwartz wherein biomolecules linked to solid support can be linked to other proteins or analytes (e.g. antigen) by conventional methods, it would be obvious to one of ordinary skill in the art to immobilize a biomolecule (e.g. antibody, receptor or proteins) through a cleavable linkage to solid phase to capture complementary binding partner (e.g. antigen or ligand) or to bind to carriers (such as in the case of protein polysaccharide conjugate) for subsequent cleavage of the binding complex from the solid surface for further diagnostic and therapeutic applications. From the teaching of cleavable attachment of biomolecuels on solid support (Schwartz *et al*), one of ordinary skill in the art can easily envision preparing the conjugate vaccine (i.e. conjugate of a protein with a bacterial polysaccharide) first on a solid support and then cleaving the conjugate from the solid support because this process would require less step to acquire the conjugate vaccine. It is the examiner's position that given the Schwartz discussion of the applicability of the cleavable linkage technology to the conjugation of a wide variety of reactants such as solid surfaces and biomolecules as discussed above, the sequential attachment of a "Second Macromolecule" to a surface-immobilized "First Macromolecule", as claimed, would constitute a routine variation in the sequence of performance of a

known set of steps conventionally used to attach biomolecules to each other and/or to solid surfaces via acid cleavable hydrazone bonds as described by Schwartz.

Further, prior art is not limited just to the references being applied, but includes the understanding of one of ordinary skill in the art. The prior art reference (or references when combined) need not teach or suggest all the claim limitations. The "mere existence of differences between the prior art and an invention does not establish the invention's nonobviousness." The gap between the prior art and the claimed invention may not be "so great as to render the [claim] non-obvious to one reasonably skilled in the art." In determining obviousness, neither the particular motivation to make the claimed invention nor the problem the inventor is solving controls. The proper analysis is whether the claimed invention would have been obvious to one of ordinary skill in the art after consideration of all the facts. Factors other than the disclosures of the cited prior art may provide a basis for concluding that it would have been obvious to one of ordinary skill in the art to bridge the gap.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on 571-272-0823. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shafiqul Haq/
Examiner, Art Unit 1641